PATENT COOPERATION TREATY

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INTERNATIONAL SEARCHING AUTHORITY

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To:

23/12

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/006426	International filing date *(day/month/year)* 14.06.2004
Priority date *(day/month/year)* 16.06.2003	
International Patent Classification (IPC) or both national classification and IPC A61K39/102, A61K39/385, A61K39/39, A61P31/04, A61K9/51	
Applicant GLAXOSMITHKLINE BIOLOGICALS S.A.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 35, 49, 50 (in part), 42

because:

☒ the said international application, or the said claims Nos. 35, 49, 50 (in part) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 42 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-9, 12, 13, 20-22, 25, 28, 31, 32, 37, 38, 42, 44, 45, 47, 51-57
	No:	Claims	1-4, 10, 11, 14-19, 23-24, 26-27, 29, 30, 33-36, 39-41, 43, 46, 48-50, 58, 59
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-59
Industrial applicability (IA)	Yes:	Claims	1-34, 36-48, 51-59
	No:	Claims	

2. Citations and explanations

see separate sheet

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Item III

1 **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability (Rule 67.1, PCT)**

Claims 35, 49, 50 relate to subject matter considered by this Authority to be covered by the provisions of **Rule 67.1(iv), PCT.** Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims **(Article 34(4)(a)(i), PCT).**

2 **Clarity problems affecting the examination (Article 6, PCT)**

2.1 The wording of **claim 42** is unclear in the sense of **Article 6, PCT** as far as relating to "composition is added extemporaneously". Due to this unclarity at present no examination of novelty and inventive step is possible.

Item V

1 Reference is made to the following documents:

D1 GUPTA R K ET AL: "BIODEGRADABLE POLYMER MICROSPHERES AS VACCINE ADJUVANTS AND DELIVERY SYSTEMS" DEVELOPMENTS IN BIOLOGICAL STANDARDIZATION, KARGER, BASEL, CH, vol. 92, 1998, pages 63-78, XP001015412 ISSN: 0301-5149

D2 BOEHM GÉRARD ET AL: "On technological and immunological benefits of multivalent single-injection microsphere vaccines." PHARMACEUTICAL RESEARCH. SEP 2002, vol. 19, no. 9, September 2002 (2002-09), pages 1330-1336, XP002306393 ISSN: 0724-8741.

D3 WO 98/17310 A (DIMMINACO AG S A LTD ; HILGERS LUUK (NL)) 30 April 1998 (1998-04-30)

D4 NICOL F ET AL: "Poly-L-glutamate, an anionic polymer, enhances transgene expression for plasmids delivered by intramuscular injection with in vivo electroporation" GENE THERAPY, vol. 9, no. 20, October 2002 (2002-10), pages 1351-1358, XP002306397 ISSN: 0969-7128

D5 MILAS LUKA ET AL: "Poly(L-glutamic acid)-paclitaxel conjugate is a potent enhancer of tumor radiocurability." INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS, vol. 55, no. 3, 1 March 2003 (2003-03-01), pages 707-712, XP002306398 ISSN: 0360-3016

D6 YANG ZHIQIANG ET AL: "Poly(glutamic acid) poly(ethylene glycol) hydrogels prepared by photoinduced polymerization: Synthesis, characterization, and preliminary release

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studies of protein drugs" JOURNAL OF BIOMEDICAL MATERIALS RESEARCH, vol. 62, no. 1, October 2002 (2002-10), pages 14-21, XP002306399 ISSN: 0021-9304

D7 WO 02/00249 A (DESMONS PIERRE MICHEL ; LEMOINE DOMINIQUE (BE); SMITHKLINE BEECHAM BIO) 3 January 2002 (2002-01-03)

D8 DATABASE MEDSAFE [Online] NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY; 2002, GLAXOSMITHKLINE NZ LTD: "Datasheet - Hiberix" XP002306401 retrieved from HTTP://WWW.MEDSAFE.GOVT.NZ/PROFS/DATASHEET/H/HIBERIXINJ.HTM

2 Novelty (Article 33(2), PCT)

2.1 **D1** teaches that in recent years biodegradable polymer microspheres have received much attention for the purposes of controlled release of antigens (Ag), (I) to reduce the number of doses needed for primary immunization to as few as a single dose and (II) to target an Ag to microfold cells on mucosal surfaces after oral administration or to Ag-presenting cells after parenteral inoculations. A variety of vaccine Ags have been encapsulated in microspheres usually composed of poly (lactic/glycolic) acid (PLGA). Additionally, another adjuvant may be incorporated inside microspheres together with the Ag, further enhancing or modulating the immune response to the desired type. The major problems in developing controlled-release vaccines include instability of vaccine Ags during micro-encapsulation, storage and subsequent hydration. Tetanus toxoid (TT) and Haemophilus influenzae type b capsular polysaccharide conjugated to TT (Hib-T) is encapsulated inside PLGA microspheres and the Ab levels in mice are evaluated. A single injection of these micro-encapsulated vaccines elicited high Ab levels which persists for several months. The Ab levels are similar or superior to those elicited by conventional formulations of AlPO4-adsorbed TT or soluble Hib-T conjugate vaccine.

remark: although **D1** does not explicitly mention the parameters set out in **claims 14-18, 59** it is assumed that these parameters are implicitly disclosed.

Thus, in view of the teachings of **D1**, the subject matter of **claims 1-4, 10, 11, 15-19, 23, 26, 27, 29, 30, 34-36, 39-41, 43, 46, 48-50, 58, 59** would not appear to be novel in the sense of **Article 33(29, PCT.**

2.2 **D2** discloses mono- /multivalent vaccines of Haemophilus influenzae type b (Hib)-TT conjugate, diphtheria toxoid (DT), tetanus toxoid (TT), and pertussis toxin (PT) in poly (lactate) and poly(lactic-coglycolate) microspheres. The influence of coencapsulated Ag

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and excipients on Ag loading, release, and stability is examined. Strong and sustained Ab responses are elicited after a single injection of tetravalent microsphere vaccines (DT + TT + PT + Hib) in guinea pigs.

remark: although **D2** does not explicitly mention the parameters set out in **claims 14-18, 59** it is assumed that these parameters are implicitly disclosed.

Thus, in view of the teachings of **D2**, the subject matter of **claims 1-4, 10, 11, 14, 16-19, 23, 24, 26, 27, 30, 33-36, 49, 50, 58, 59** would not appear to be novel in the sense of **Article 33(29, PCT**.

2.3 It would appear that no documents are comprised in the available prior art disclosing the subject matter of **claims 5-9, 12, 13, 20-22, 25, 28, 31, 32, 37, 38, 42, 44, 45, 47, 51-57**. Therefore, the subject matter of said claims would appear to be novel in the sense of **Article 33(2), EPC.**

3 Inventive step (Article 33(3), PCT)

The subject matter of **claims 5-9, 12, 13, 20-22, 25, 28, 31, 32, 37, 38, 42, 44, 45, 47, 51-57** would not appear to involve an inventive step in the sense of **Art. 33(3), PCT** for the following reasons:

D1 is considered to be the closest prior art and teaches that in recent years biodegradable polymer microspheres have received much attention for the purposes of controlled release of antigens (Ag), (i) to reduce the number of doses needed for primary immunization to as few as a single dose and (ii) to target an Ag to microfold cells on mucosal surfaces after oral administration or to Ag-presenting cells after parenteral inoculations. A variety of vaccine Ags have been encapsulated in microspheres usually composed of poly (lactic/glycolic) acid (PLGA). Additionally, another adjuvant may be incorporated inside microspheres together with the Ag, further enhancing or modulating the immune response to the desired type. The major problems in developing controlled-release vaccines include instability of vaccine Ags during micro-encapsulation, storage and subsequent hydration. Tetanus toxoid (TT) and Haemophilus influenzae type b capsular polysaccharide conjugated to TT (Hib-T) is encapsulated inside PLGA microspheres and the Ab levels in mice are evaluated. A single injection of these micro-encapsulated vaccines elicited high Ab levels which persists for several months. The Ab levels are similar or superior to those elicited by conventional formulations of AlPO4-adsorbed TT or soluble Hib-T conjugate vaccine.

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3.1 claims 5-9, 12, 13

The subject matter of **claims 5-9, 12, 13** differs from **D1** in that it discloses the use of different polyanionic polymers for microencapsulation.
Therefore, the technical problem is to provide alternative polyanionic polymers for microencapsulation of Hib.
The claimed solution is the use of the specific polyanionic polymers listed in **claims 5-9, 12, 13.**

Starting from the closest prior art, a skilled person would be aware, that a variety of different polyanionic polymers can be used for microencapsulation-sustained release formulations. Possible alternative compounds are well known in the art (c.f. **D3-D6**).
Consequently, the subject matter of **claims 5-9, 12, 13** would not appear to involve an inventive step in the sense of **Article 33(3), PCT** unless an unexpected or synergistic effect compared to the compositions used in prior art is demonstrated.

3.2 claims 20-22, 25, 44, 45, 47

The subject matter of **claims 20-22, 25** differs from **D1** in that it discloses the incorporation of one or further Ag into the composition comprising the Ag disclosed in said claims.
Therefore, the technical problem is to provide alternative multivalent vaccine compositions.
The claimed solution is the use of the specific vaccine compositions according to **claims 20-22, 25.**

The skilled person is aware, that different antigens can be combined in a composition in order to achieve a broad protection.
The closest prior art already discloses such multivalent microsphere vaccines, other possible combinations are evident from the different combinations already on the market or published (c.f. e.g. **D7, D8** - a short summary is given at the end of the paragraph).
Consequently, the subject matter of **claims 20-22, 25** would not appear to involve an inventive step in the sense of **Article 33(3), PCT.**

D7 claims a multi-valent immunogenic composition comprising a conjugate of a carrier protein (tetanus toxoid, diphtheria toxoid, CRM197, protein D...) and the capsular polysaccharide of H. influenza type B, wherein said composition additionally comprises 2 or more further bacterial polysaccharides (e.g. N. meningitidis Y or W polysaccharide,

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Streptococcus pneumoniae 1...).
One specific DTPw composition disclosed comprises: TT, DT: Pw HepB (perferably adsorbed onto Al-phosphate), Hib (preferably conjugated onto TT and/or unadsorbed), MenA (pref. conjugated onto protein-D) and MenC (pref. conjugated onto protein D).
Combination vaccines according to **D7** require substantially lower doses of Hib to obtain at least equivalent Ab titers. **D7** mentions, that due to the known effect of carrier suppression, it is advantageous if in each of the compositions of the invention the polysaccharide Ag contained therein are conjugated to more than one carrier (c.f. p 3, l 2-7, 23-33; p 5, l 18-21; claims 12-15, 19, 20, 27-29).

D8 discloses that Hiberix (unadsorbed Hib-TT) can be mixed in the same syringe with SmithKline Beecham vaccines Infanrix (DTPa vaccine), Tritanrix™ (DTPw vaccine) or Tritanrix™-HB (DTPw-HB vaccine).

3.3 claim 28

The specific amount of adjuvant in the range of 100-1000 micrograms per 0.5 mL dose is a little bit higher to the one described in the closest prior art, however, in the same range. Consequently, the subject matter of **claim 28** would not appear to involve an inventive step in the sense of **Article 33(3), PCT** unless an unexpected or synergistic effect compared to the compositions used in prior art is demonstrated.

3.4 claims 31, 32

The specific embodiments of **claims 31, 32** would not appear to involve an inventive step in the sense of **Art. 33(3), PCT** combining the teachings of the closest prior art with the teachings of **D7** (for a short summary see above).

3.5 claims 37, 38

The subject matter of **claim 37** differs from **D1** in that it describes a method reducing immunological interference of Haemophilus influenzae B capsular polysaccharide or oligosaccharide characterized by the steps of 1) adsorbing the one or more further antigens onto the adjuvant; 2) adding a polyanionic polymer to said one or more further antigens; and 3) then adding an immunogenic composition comprising PRP to said one or more further antigens.
The technical problem is to provide a method for reducing the immunological interference

of Haemophilus influenzae B capsular polysaccharide or oligosaccharide, i.e. to provide an improved vaccine formulation.
The claimed solution is a method characterized by the steps of 1) adsorbing the one or more further antigens onto the adjuvant; 2) adding a polyanionic polymer to said one or more further antigens; and 3) then adding an immunogenic composition comprising PRP to said one or more further antigens.

It would appear, that none of the experiments provided in the application use the claimed method. *Example 1* provides data on Hib-PLG formulations; *Example 2* analyses the effect of flocculation/aggregation in Infanrix, Tritanix formulations; *Example 3* provides data from a phase II clinical trial showing that DTPa-HBV-IPV (licensed formulation - i.e. not microencapsulated with polyanionic polymers) + Hib-TT-PLG results in a slightly higher (protective) response compared to DTPa-HBV-IPV/Hib or DTPa-HBV-IPV and Hiberix, respectively.
However, no data showing a surprising/synergistic/advantageous effect of a composition prepared by the claimed method, i.e. comprising step 2) of the method is provided.
Thus, at present it would appear to be not possible to establish whether the subject matter of **claims 37, 38** involves an inventive step in the sense of **Art. 33(3), PCT**.

3.6 claims 51-57

Due to the fact that the single compounds are used in (a) known therapeutic method(s)s or methods which do not appear to involve an inventive step and that it is a common practise to offer therapeutic/diagnostic reagents used in a therapeutic method in form of kits, the subject matter of **claims 51-57** also does not appear to involve an inventive step in the sense of **Article 33(3), PCT**.

4 further remarks

4.1 Contrary to the requirements of **Rule 5.1(a)(ii), PCT**, the relevant background art disclosed in **D1-D2**, would not appear to be mentioned/discussed in the description, nor are these documents identified therein **(Guidelines 4.05)**.

4.2 The vague statements in the description on p 19, l 31 imply that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity **(Article 6, PCT)** when used to interpret them.

4.3 Expressions like "preferably", "for example", "such as" or "more particularly" are

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considered to have no limiting effect on the scope of the claim (c.f. **claim 6, 9, 14, 16, 17, 18, 20, 25, 33, 37, 43, 49, 51**): that is to say, the feature following any such expression is to be regarded as entirely optional (c.f. **Guidelines 5.40**).

4.4 The scope of **claims 34, 35, 36** relating to a therapeutic use of the compositions of **claims 1-33** also comprises salts of anionic constitutional repeating units (c.f. **claim 5, 7**) which are not suitable for pharmaceutical use.

4.5 The repeated use of the non restrictive term/phrase "about", "around" or similar terms introduces ambiguity into **claims 14, 18** (c.f. **PCT Guidelines, Section IV, III-4.5a**).